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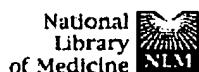
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1: Peptides 1997;18(4):551-7

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## Several receptors mediate the antisecretory effect of peptide YY, neuropeptide Y, and pancreatic polypeptide on VIP-induced fluid secretion in the rat jejunum in vivo.

**Souli A, Chariot J, Voisin T, Presset O, Tsocas A, Balasubramaniam A, Laburthe M, Roze C.**

INSERM U410, Faculte de Medecine X. Bichat, Paris, France.

Several Y receptor subtypes have been cloned and/or pharmacologically characterized that mediate the effects of the regulatory peptides peptide YY (PYY), neuropeptide Y (NPY), and pancreatic polypeptide (PP). These peptides possess antisecretory properties on the intestine. This effect can be blocked in vivo by neural antagonists, suggesting the intervention of neural receptors, although epithelial PYY-preferring receptors have been evidenced on jejunal crypt cells. The purpose of the present experiments was to compare the antisecretory properties in vivo of a series of PYY and NPY derivatives with various affinities for different Y receptor subtypes, in order to determine which subtypes were involved. A model of VIP-stimulated secretion by rat jejunal loops was used. The results were compared with the binding affinities for PYY-preferring receptors determined on rat jejunal crypt cell membranes. Full-length PYY(1-36) was about three times more potent than NPY(1-36), and 10 times more potent than PP in the low dose range. PP, however, had a low efficacy limited to about 50% inhibition of VIP effect. Both Y1 agonists ([Leu31, Pro34]PYY and [Leu31, Pro34]NPY), and Y2 agonists [C-terminal fragments ranging from PYY (3-36) and NPY(3-36) to PYY(22-36) to NPY (22-36)] displayed potent antisecretory properties. PYY derivatives and fragments were always more potent than their respective NPY counterparts. In contrast, Y1 derivatives and PP had very low affinity for the epithelial PYY receptor as measured in vitro by radioreceptor assay. These data suggest that the antisecretory effect of PYY/NPY/PP peptides in vivo involves the effects of several receptors: a Y2-like, PYY-preferring receptor identical to the epithelial receptor, a Y1-like receptor, and a third receptor with high affinity for PP.

PMID: 9210175 [PubMed - indexed for MEDLINE]



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Γ 1: J Med Chem 2000 Sep 7;43(18):3420-7

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PPY receptor affinity or the proabsorptive potencies in dogs. These differences could be due to species effects and/or the involvement of multiple receptors and neuronal elements in controlling the *in vivo* activity of PPY compounds. PPY(22-36) analogues exhibited good affinity for neuronal Y2 receptors but poor affinity for Y1 receptors. Also, crucial analogues in this series hardly bound to Y4 and Y5 receptors. In summary, we have developed PPY(22-36) analogues which, via interacting with intestinal PPY receptors, promoted potent and long-lasting proabsorptive and antisecretory effects in *in vivo* models. These compounds or analogues based on them may have useful clinical application in treating malabsorptive disorders observed under a variety of conditions.

PMID: 10978189 [PubMed - indexed for MEDLINE]

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**Peptide YY inhibits growth of human breast cancer in vitro and in vivo.**

Grise KR, Rongione AJ, Laird EC, McFadden DW.

University of California at Los Angeles Medical Center, Los Angeles, California, 90095, USA.

**BACKGROUND.** Hormonal manipulation is important in the treatment of breast cancer. Gastrointestinal hormones may have antiproliferative effects on malignancies arising outside the gastrointestinal tract. Peptide YY (PYY) suppresses growth of, and levels of, intracellular cyclic adenosine monophosphate (cAMP) in pancreatic adenocarcinoma. We hypothesized that PYY would inhibit growth of breast cancer. **MATERIALS AND METHODS.** MCF-7 human breast infiltrative ductal carcinoma cells in 96-well plates were treated with PYY at 1.25 pmol/ml. Control wells received an equal volume of bovine serum albumin to mimic experimental conditions. In vitro survival was determined by MTT assays, which reflect cell viability by measuring mitochondrial NADH-dependent dehydrogenase activity. MCF-7 cells in six-well plates were treated with PYY or albumin as described above. Intracellular cAMP levels in cell lysates were determined with a tritiated cAMP assay. One million MCF-7 cells were injected into mammary fat pads of 20 female athymic nude mice. Pellets releasing PYY at 400 pmol/kg/h were placed subcutaneously in 10 mice 24 h prior to cell inoculation. Tumors were harvested after 21 days, weighed, and measured with vernier calipers. **RESULTS.** PYY reduced in vitro growth by 40% ( $P < 0.001$ ). Intracellular cAMP levels in PYY-treated cells were 62.4% less than those of controls ( $P < 0.001$ ). Tumors from control mice weighed twice as much as those from PYY-treated mice ( $P < 0.006$ ); volume of PYY-exposed tumors was one-third that of controls ( $P < 0.005$ ). **CONCLUSIONS.** PYY inhibits growth of breast cancer in vitro and in vivo and may be of benefit in the treatment of this malignancy. The reduction in intracellular cAMP levels may contribute to the observed suppression of cell proliferation. Copyright 1999 Academic Press.

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1: Pancreas 1992;7(5):595-600      Related Articles. Books

### **Evidence for a direct inhibitory effect of PYY on insulin secretion in rats.**

**Bertrand G, Gross R, Roye M, Ahren B, Ribes G.**

Faculte de Medecine, Laboratoire de Pharmacologie et Pharmacodynamie, CNRS URA 599, Montpellier, France.

Peptide YY (PYY) has been shown to inhibit stimulated insulin secretion under *in vivo* conditions in the mouse, the rat, and the dog. In the present study, we investigated the effects of PYY on insulin secretion from the isolated perfused rat pancreas and isolated rat islets. In isolated pancreas perfused in presence of 8.3 mM glucose, PYY at 10(-10) and 10(-9) M, but not at 10(-8) M, inhibited insulin secretion. In the presence of 5.5 mM glucose, PYY (10(-9) M) did not modify basal insulin release but reduced the biphasic insulin response to arginine (10 mM). PYY also markedly reduced the pancreatic vascular flow rate; this effect was observed at all three concentrations tested in a dose-dependent manner. In isolated islets, glucose (15 mM)-stimulated insulin secretion was inhibited by PYY at 10(-7) M. We conclude that in the perfused rat pancreas, PYY inhibits insulin secretion and induces vasoconstriction without a causal relationship. In addition, our results on isolated islets suggest that the inhibitory action of PYY on insulin secretion is exerted through a direct islet action.

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